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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/095,536	06/10/1998	JOHN A. KINK	OPHD-03282	9749

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EXAMINER	
HISSONG, BRUCE D	
ART UNIT	**PAPER NUMBER**
1646	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/095,536	KINK, JOHN A.	
	Examiner	Art Unit	
	Bruce D. Hissong, Ph.D.	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10/19/2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *49-57* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *49-57* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/19/2007 has been entered.

2. Claims 49-57 are currently pending and are the subject of this office action.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 49-57 *remain rejected* under 35 USC § 103(a) as being obvious in view of the combination of Skurkovich et al ("Skurkovich"), Starnes et al ("Starnes"), and Doherty et al ("Doherty"), as set forth on pages 2-4 of the office action mailed on 8/29/2007.

In the response received on 10/19/2007, the Applicant argues that the claims are not obvious in view of the cited combination for several reasons. First, the Applicant argues that Skurkovich is non-analogous art because it is drawn to treatment of autoimmune disease and AIDS, and not sepsis, and is directed towards solving a different problem than that of the instant invention. Thus, one of ordinary skill in the art would not look to Skurkovich for guidance to treat sepsis. The Applicant also argues that no rationale is provided to explain why a person of ordinary skill in the art would be motivated to use the composition of Skurkovich to treat sepsis based on the teachings of Starnes and Doherty, which teach administration of single antibodies, rather than the claimed composition. Furthermore, the Applicant argues that *In re Keller* and *In re Merck & Co* were improperly cited in the previous office action because

the Applicant did in fact provide arguments regarding all three of the cited references. The Applicant further argues that the deficiencies of Starnes and Doherty cannot be remedied by combination with Skurkovich without a basis for such combination, which is consistent with *In re Rouffet*, which states that references must be evaluated individually for their specific motivation to one skilled in the art, without hindsight, before the combination can be made. Finally, the Applicant argues that the data presented in Table 5 of the specification shows an unexpected result due to the degree of improvement (100% protection) afforded by the combination of all three antibodies. The Applicant alleges that this data was not taken into consideration by the Examiner in the previous office action, and submits a declaration by Dr. Stafford which discusses the percent survival numbers in Table 5 and emphasizes that the results do not show some benefit, but rather shows excellent results compared to single antibody preparations or double antibody combinations. The declaration further emphasizes that these results are not due to differences in the timing of administration.

These arguments have been fully considered and are not persuasive. In response to Applicant's arguments that Skukovich is non-analogous art, it is noted that claim 49 is not drawn to a method of treating sepsis, but rather to a method of administering anti-IFN-g, anti-TNF-a, and anti-IL-6 antibodies to a mammal having a plurality of symptoms of sepsis. Skurkovich teaches administration of the same combination for treatment of autoimmune disorders and AIDS. Because it would be expect that AIDS would be characterized by fever and organ failure, Skurkovich teaches treatment of patients with a plurality of symptoms of sepsis, and thus seeks to solve the same problem as set claims 49-50. Additionally, Skurkovich teaches that the combined anti-cytokine therapy reduces inflammation in patients, and was safely tolerated by said patients (see Examples 3-7 and claim 6). The Applicant argues that Opal *et al* (*J. Infect. Dis.*, 1996, 173:1415-1421) teaches that combined anti-cytokine therapy "may exacerbate systemic infection and worsen [the] outcome in experimental sepsis", and thus teaches away from treatment with the claimed compositions. However, it is noted that Opal *et al* discusses administration of IL-1 receptor antagonist and TNF binding protein, and is silent regarding any effects of combined anti-IFN-g, anti-IL-6, and/or anti-TNF-a administration. Furthermore, Skurkovich teaches effective treatment by administering such combinations, and does not disclose any harmful effects.

Therefore, because Starnes and Doherty collectively teach that anti-IL-6, anti-TNF-a, and anti-IFN-g are individually useful and effective in treating sepsis, or of relieving symptoms of sepsis, and Skurkovich teaches that combinations of these antibodies relieves inflammation and would treat symptoms of sepsis, one of ordinary skill in the art would be motivated to combine the three references in order to practice the claimed invention.

The Applicant also argues that *In re Keller* and *In re Merck* were not properly cited in the previous office action. Upon further reconsideration, the Examiner acknowledges that the Applicant did indeed address all three references. However, as set forth in the preceding paragraphs, the disclosures of Starnes, Doherty, and Skurkovich, when assessed individually, as required by *In re Rouffet* (cited in Applicant's response received 10/19/2007), would provide one of skill in the art with the motivation to combine all three antibodies because Starnes and Doherty show that each antibody is individually effective in treating sepsis, and Skurkovich shows combined administration is safely tolerated.

Finally, Applicant's arguments of unexpected results, and the declaration by Dr. Stafford regarding said results, are noted. Briefly, the Applicant and Dr. Stafford state that the 100% protection afforded by combined anti-IFN-g, anti-IL-6, and anti-TNF-a administration is unexpected in view of the limited success of administration of single antibodies, or combinations of only two antibodies. Therefore, due to these unexpected results, the claims cannot be obvious in view of the prior art.

It is noted, however, that Table 5 discloses only one double antibody combination, anti-IL-6 and anti-IFN-g, but does not present data showing the other possible combinations, namely anti-IL-6 and anti-TNF-a, and anti-IFN-g and anti-TNF-a. Thus, Applicants arguments, and the declaration by Dr. Stafford, are not convincing due to the lack of appropriate controls. Both Starnes and Doherty disclose that administration of anti-TNF-a antibodies is useful for treating sepsis (Fig. 4 of Starnes, Fig 3. in Doherty). Doherty teaches that TNF-a is an important mediator of sepsis (p. 1666, 1st paragraph), and that IFN-g is necessary for the toxic and lethal effects of both LPS and TNF-a (p. 1668-1669), and that IFN-g increases LPS-stimulated production of TNF-a *in vitro*. Doherty also teaches that IFN-g is an "obligatory comediator of TNF-a activity" in endotoxemia (p. 1669, last paragraph). Furthermore, Doherty describes a synergistic effect between IFN-g and TNF-a *in vitro*, as well as *in vivo*, and the combination of IFN-g and TNF-a is synergistic for production of IL-6 (p. 1669, 2nd column, 1st paragraph). Thus, based on the disclosures of Starnes and Doherty, one of ordinary skill in the art would expect that neutralization of both IFN-g and TNF-a would be highly effective in treating sepsis. However, Table 5 of the instant application does not present data showing the effects of combined anti-IFN-g and anti-TNF-a, so it cannot be said with certainty that the results derived from neutralization of all three antibodies is unexpected, given the teachings of Doherty regarding IFN-g and TNF-a, the disclosure of Starnes, which shows beneficial effects of IL-6 neutralization (Fig. 4).

It is also noted that although claims 51, 54, and 57 have been amended to recite the limitation that the claimed compositions comprise avian antibodies, these claims are obvious in view of Skurkovich, Starnes, and Doherty because regardless of the source of antibody, the recited references provide the

motivation to treat sepsis by co-administering anti-IFN-g, anti-TNF-a, and anti-IL-6, and therefore it would be obvious to create a composition comprising these antibodies from any source. In the absence of evidence to the contrary, it would be expected that antibodies from an avian source would neutralize the recited cytokines in the same manner as antibodies from murine or other sources. Because the USPTO does not have the facilities for testing the avian antibodies of the instant invention, the burden is on the applicant to show a novel and unobvious difference between the claimed antibodies and those of the prior art. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

Therefore, for the reasons set forth above and in the previous office action, the claims of the instant invention are obvious in view of Skurkovich, Starnes, and Doherty.

Conclusion

No claim is allowable.

All claims are drawn to the same invention claimed in the parent application prior to the filing of this Continued Prosecution Application under 37 CFR 1.53(d) and could have been finally rejected on the grounds and art of record in the next Office action. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing under 37 CFR 1.53(d). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no, however, event will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bruce D. Hissong, Ph.D., whose telephone number is (571) 272-3324. The examiner can normally be reached M-F from 8:30 am - 5:00 pm. If attempts to reach the examiner by telephone are

unsuccessful, the examiner's supervisor, Gary Nickol, Ph.D., can be reached at (571) 272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Bruce D. Hissong
Art Unit 1646

/Robert Landsman/
Primary Examiner, Art Unit 1647